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Pulmonary Fibrosis and Proteostasis

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Commentary

The proteostasis network is made up of several specialized proteins that are required for the correct operation of processes that regulate the life cycle of all cellular proteins. Through the action of molecular chaperones, newly translated proteins are folded into their natural state and transported to specified subcellular sites. Damaged or no longer required proteins are destroyed by the ubiquitin-proteasome or lysosomal degradation processes. The intracellular proteome faces a major challenge when the proteostasis network is disrupted at any point, resulting in a relative imbalance in functional levels of critical proteins in subcellular compartments and the accumulation of misfolded or damaged proteins that are prone to aggregate or precipitate in the remarkably protein-rich intracellular environment. The molecular "chaperone" in humans is made up of 332 genes that play a variety of roles in protein folding. The Heat Shock Protein (HSP) family, as well as proteins involved in organelle-specific folding in the endoplasmic reticulum and mitochondria, is among these chaperones. Chaperones are expressed in most cells continually, although they are strongly activated in response to environmental (e.g., heat shock) or organelle-specific stress (e.g., endoplasmic reticulum stress or the mitochondrial unfolded protein response). Many lung disorders, including pulmonary fibrosis, may be caused by proteostatic stress in the lung epithelium, according to genetic studies. Mutations in the gene encoding SFTPC, which induce protein misfolding, have been found in families with higher rates of idiopathic pulmonary fibrosis. Hermansky-Pudlak syndrome is caused by an autosomal-recessive mutation that causes a vesicular trafficking impairment and is linked with highly penetrant lung fibrosis. Although there is no direct evidence of a protein folding error, a frequent variant SNP in the promoter region of the gene encoding an abundantly expressed mucin, MUC5B, has been linked to greater protein expression and a higher risk of pulmonary fibrosis. As part of an adaptive response, the prolonged proteostatic stress associated with these mutations may stimulate the production of chaperones in the lungs. Genetic deletion of HSP70 (Hspa1a) in mice has been shown to increase sensitivity to bleomycin-induced fibrosis, supporting this notion. We report on the expression of HSP70 in lung tissues and primary human lung fibroblasts acquired from patients with pulmonary fibrosis in this edition of the Journal. In lung tissue from patients with pulmonary fibrosis compared to normal control subjects and primary cultured fibroblasts from the lungs of patients with pulmonary fibrosis, the expression of constitutive and inducible HSP70 was reduced, contrary to expectations. The researchers went on to show that the profibrotic cytokine TGF or viral transfection of IGFBP5 lowered both constitutive and inducible HSP70 production. They believe that by removing HSP70 from the fibrotic milieu, an inhibitory effect on TGF signalling was abolished, allowing lung fibroblasts to produce more matrix proteins. Global deletion of the inducible form of HSP70 worsened bleomycin-induced fibrosis in mice, indicating that HSP70 plays a protective function in fibrosis. Our research adds to the growing body of evidence linking proteostasis network malfunction to the development of fibrosis while also raising new questions. Most critically, the researchers believe that signalling mediated by profibrotic cytokines in the microenvironment may suppress chaperone expression, worsening proteostatic stress and potentially producing a self-sustaining fibrosis cycle. However, significant additional effort will be required before such a judgement can be reached. Although chaperones are found in almost all cells, their regulation during stress is likely to be cell-type specific. To answer these questions, careful research in which chaperones are eliminated within specific cell types will be required. Furthermore, while HSP70 expression was reduced in end-stage fibrotic tissues studied by We, it is unclear if this represents an early event in fibrosis aetiology or later phases of the disease. For example, acute expression of a cystic fibrosis-causing mutation of the CFTR gene in airway epithelial cells induces an adaptive chaperone response, but persistent expression results in widespread protein folding failure. Furthermore, the finding that reduced HSP70 expression persists in lung fibroblasts from pulmonary fibrosis patients after removal from the fibrotic microenvironment

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suggests that epigenetic modifications impair chaperone responses; however, the mechanisms behind this finding are unknown. And research also raises concerns regarding ageing's increased susceptibility to pulmonary fibrosis. A large body of evidence implies that proteostasis network disruption is a primary driver of age-related phenotypes, which may be programmed by conserved signalling events. Also discovered lower mRNA expression of chaperones in normal ageing and dementia patients in a study of human brains. Adult mice lacking inducible HSP70 are marginally more prone to fibrosis than juvenile mice, according to us. To answer these problems, systematic research examining both the expression and function of proteostasis genes during ageing would be required.